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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE (57) Abstract The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.		

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TITLE OF THE INVENTION**INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE****BACKGROUND OF THE INVENTION**

5 The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon
10 growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M.
15 Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth
20 stimulatory signal.

 Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus
25 contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein
30 transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation.

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Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which
5 is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify
10 other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl et al., *Science*, 260:1934-1937 (1993) and G.L. James et al., *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of
15 farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl et al., *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl et al., *Nature Medicine*, 1:792-797 (1995).

20 Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock et al., *ibid*; Casey et al., *ibid*; Schafer et al., *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including
25 farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss et al., *Cell*, 62:81-88 (1990); Schaber et al., *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer et al., *Science*, 249:1133-1139 (1990); Manne et al., *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate
30 biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor

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of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of

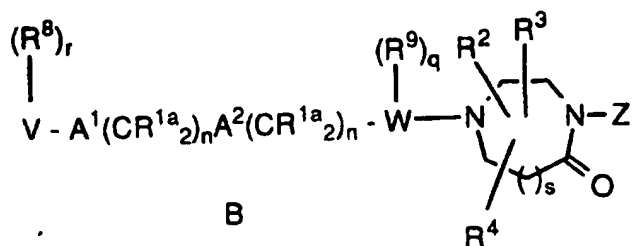
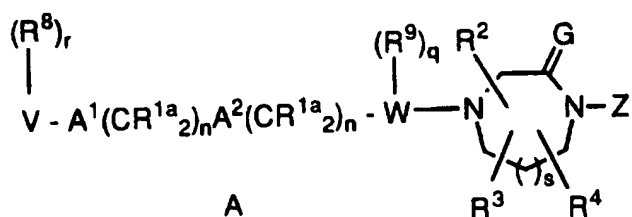
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this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

5 The present invention comprises peptidomimetic piperazine-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid
10 autooxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

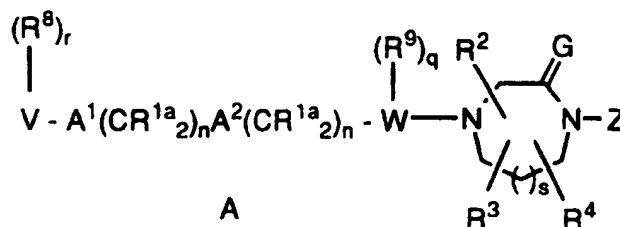
15 The compounds of this invention are illustrated by the formulas A and B:



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DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:

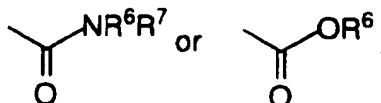


wherein:

R^{1a} is selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;
- 20

R² and R³ are independently selected from: H; unsubstituted or substituted C₁₋₈ alkyl, unsubstituted or substituted C₂₋₈ alkenyl, unsubstituted or substituted C₂₋₈ alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

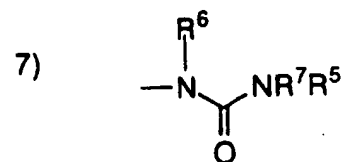
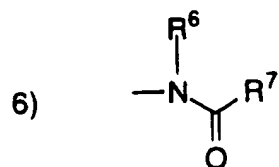
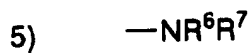


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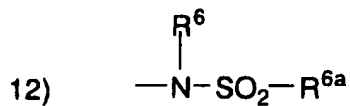
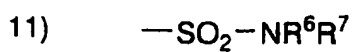
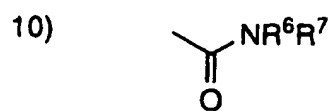
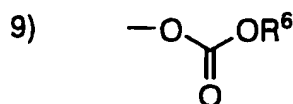
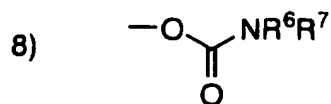
wherein the substituted group is substituted with one or more of:

- 5
- 1) aryl or heterocycle, unsubstituted or substituted with:
- a) C₁₋₄ alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- e) CN,
- f) aryl or heteroaryl,
- 10 g) perfluoro-C₁₋₄ alkyl, or
- h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃₋₆ cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},

15



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- 5 R^2 and R^3 are attached to the same C atom and are combined to form $\text{—(CH}_2)_u\text{—}$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

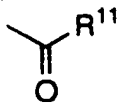
R^4 is selected from H and CH_3 ;

10

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

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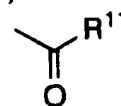
R⁶, R⁷ and R^{7a} are independently selected from: H; C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 5
- a) C₁-4 alkoxy,
 - b) aryl or heterocycle,
 - c) halogen,
 - d) HO,
 - e) 
 - f) —SO₂R¹¹, or
 - g) N(R¹⁰)₂; or

10

R⁶ and R⁷ may be joined in a ring;
R⁷ and R^{7a} may be joined in a ring;

15 R^{6a} is selected from: C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,
- e) 
- f) —SO₂R¹¹, or
- g) N(R¹⁰)₂;

20

R⁸ is independently selected from:

- 25
- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,

- 9 -

- C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 5 c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
 cyanophenyl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆
 alkenyl, C₂-C₆ alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 10 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- 15 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

25 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and
 aryl;

R¹¹ is independently selected from C₁-C₆ alkyl and aryl;

30 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

G is selected from H₂ and O;

V is selected from:

- 10 -

- 5 a) hydrogen,
 b) heterocycle,
 c) aryl,
 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
 replaced with a a heteroatom selected from O, S, and N,
 and
 e) C₂-C₂₀ alkenyl,
 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
 if A¹ is a bond, n is 0 and A² is S(O)_m;

10

W is a heterocycle;

Z is selected from: a unsubstituted or substituted group selected from
 aryl or heteroaryl, wherein the substituted group is substituted with
 15 one or more of the following:

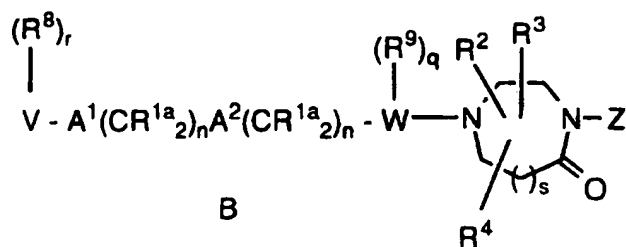
- a) C₁-4 alkyl, unsubstituted or substituted with:
 C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl,
 heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 b) aryl or heterocycle,
 c) halogen,
 d) OR⁶,
 e) NR⁶R⁷,
 f) CN,
 g) NO₂,
 h) CF₃;
 i) -S(O)_mR^{6a},
 j) -C(O)NR⁶R⁷, or
 k) C₃-C₆ cycloalkyl; ;

30 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 q is 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen; and
 s is 0 or 1;

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or the pharmaceutically acceptable salts thereof.

In a second embodiment of this invention, the inhibitors of
 5 farnesyl-protein transferase are illustrated by the formula B:

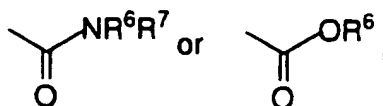


wherein:

R^{1a} is selected from:

- a) hydrogen,
- 10 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- 15 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-NR¹⁰-;
- 20

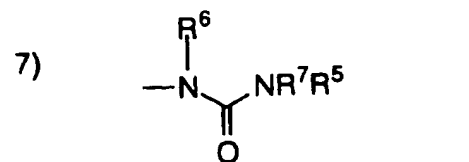
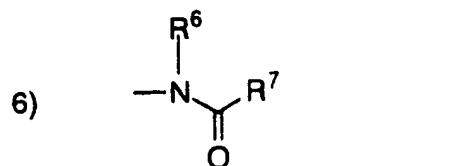
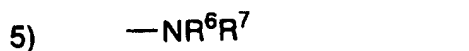
R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,
 25 unsubstituted or substituted heterocycle,



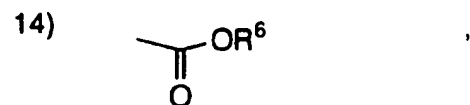
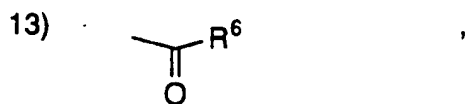
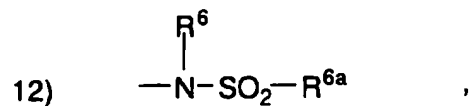
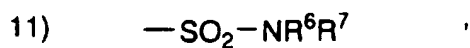
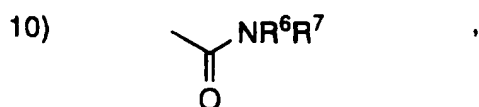
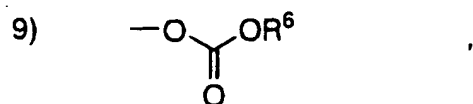
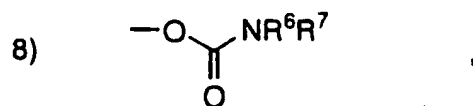
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wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁₋₄ alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁₋₄ alkyl, or
 - h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃₋₆ cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



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- 5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

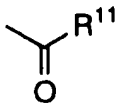
R^4 is selected from H and CH_3 ;

10

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

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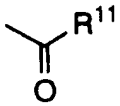
R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 5 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 10 g) N(R¹⁰)₂; or

R⁶ and R⁷ may be joined in a ring;

R⁷ and R^{7a} may be joined in a ring;

- 15 R^{6a} is selected from: C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 20 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 g) N(R¹⁰)₂;

- 25 R⁸ is independently selected from:

- a) hydrogen,
 b) aryl, heterocycle, C_{3-C10} cycloalkyl, C_{2-C6} alkenyl,

- 15 -

- C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 5 c) C1-C6 alkyl unsubstituted or substituted by aryl,
 cyanophenyl, heterocycle, C3-C10 cycloalkyl, C2-C6
 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 10 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- 15 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- c) C1-C6 alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 20 (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C1-C6 alkyl, benzyl and
 aryl;

25

R¹¹ is independently selected from C1-C6 alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
 30 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

V is selected from:

- a) hydrogen,
 b) heterocycle,

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- c) aryl,
 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 5 e) C₂-C₂₀ alkenyl,
 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

10

Z is selected from: a unsubstituted or substituted group selected from aryl or heteroaryl, wherein the substituted group is substituted with one or more of the following:

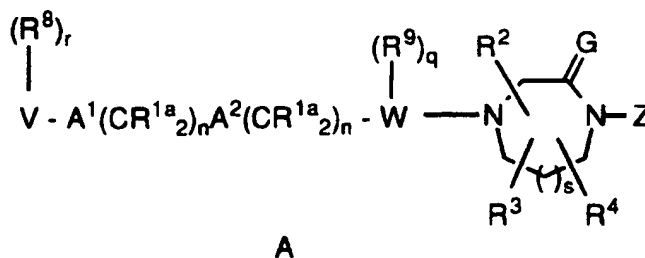
- 15 a) C₁-4 alkyl, unsubstituted or substituted with:
 C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 b) aryl or heterocycle,
 c) halogen,
 d) OR⁶,
 20 e) NR⁶R⁷,
 f) CN,
 g) NO₂,
 h) CF₃;
 i) -S(O)_mR^{6a},
 25 j) -C(O)NR⁶R⁷, or
 k) C₃-C₆ cycloalkyl; ;

- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 30 q is 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen; and
 s is 1;

or the pharmaceutically acceptable salts thereof.

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In a preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



5 wherein:

R^{1a} is independently selected from: hydrogen or C₁-C₆ alkyl;

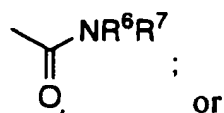
R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) aryl, heterocycle, cycloalkyl, R¹⁰O-, -N(R¹⁰)₂ or C₂-C₆ alkenyl,
 c) unsubstituted or substituted C₁-C₆ alkyl wherein the
 substituent on the substituted C₁-C₆ alkyl is selected from
 15 unsubstituted or substituted aryl, heterocycle, cycloalkyl,
 alkenyl, R¹⁰O- and -N(R¹⁰)₂;

R³ and R⁴ are independently selected from H and CH₃;

R² is H;

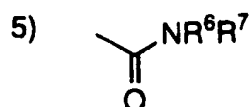
20



C₁-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 25 1) aryl,
 2) heterocycle,
 3) OR⁶,

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4) SR^{6a} , SO_2R^{6a} , or

5 and any two of R^2 , R^3 , R^4 , and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

10 H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C_{1-4} alkoxy,
- b) halogen, or
- c) aryl or heterocycle;

15 R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

- a) C_{1-4} alkoxy,
- b) halogen, or
- 20 c) aryl or heterocycle;

R^8 is independently selected from:

- a) hydrogen,
- 25 b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} perfluoroalkyl, F, Cl, $\text{R}^{10}\text{O}-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, NO_2 , $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$, and
- c) C_{1-6} alkyl substituted by C_{1-6} perfluoroalkyl, $\text{R}^{10}\text{O}-$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{N}-\text{C}(\text{NR}^{10})-$, $\text{R}^{10}\text{C}(\text{O})-$, $-\text{N}(\text{R}^{10})_2$, or $\text{R}^{11}\text{OC}(\text{O})\text{NR}^{10}-$;
- 30

R^9 is selected from:

- a) hydrogen,

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- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-, and
 - 5 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;
- 10 R¹⁰ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;
- R¹¹ is independently selected from C₁-C₆ alkyl and aryl;
- 15 A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR¹⁰-, O, -N(R¹⁰)-, or S(O)_m;
- G is selected from H₂ and O;
- 20 V is selected from:
 - a) hydrogen,
 - b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
 - 25 c) aryl,
 - d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 - e) C₂-C₂₀ alkenyl, and
- 30 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

- 20 -

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

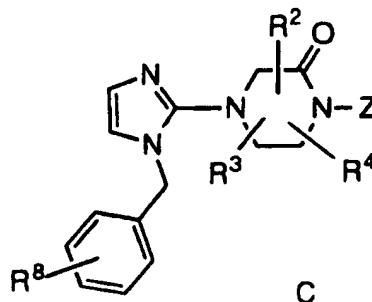
- 5 Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic heteroarylmethyl, mono- or bicyclic arylsulfonyl, mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:
- 10 1) C₁₋₄ alkyl, unsubstituted or substituted with:
- a) C₁₋₄ alkoxy,
- b) NR⁶R⁷,
- c) C₃₋₆ cycloalkyl,
- d) aryl or heterocycle,
- 15 e) HO,
- f) -S(O)_mR⁶, or
- g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 20 4) OR⁶,
- 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 25 9) -S(O)_mR⁶,
- 10) -C(O)NR⁶R⁷, or
- 11) C_{3-C6} cycloalkyl;
- 30 m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4;
- r is 0 to 5, provided that r is 0 when V is hydrogen;
- s is 0 or 1;
- t is 0 or 1; and

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u is 4 or 5;

or the pharmaceutically acceptable salts thereof.

- 5 In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula C:

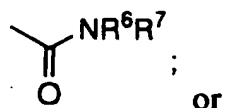


wherein:

10

R^3 and R^4 are independently selected from H and CH_3 ;

R^2 is H;



15

C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 20
- 1) aryl,
 - 2) heterocycle,
 - 3) OR^6 ,
 - 4) SR^{6a} , SO_2R^{6a} , or
 - 5) ;

and R^2 and R^3 are optionally attached to the same carbon atom;

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R⁶ and R⁷ are independently selected from:

H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

- 5 a) C₁₋₄ alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

R^{6a} is selected from:

10 C₁₋₄ alkyl or C₃₋₆ cycloalkyl,
 unsubstituted or substituted with:

- a) C₁₋₄ alkoxy,
 b) halogen, or
 c) aryl or heterocycle;

15 R⁸ is independently selected from:

- a) hydrogen,
 b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆
 perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
 (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
20 R¹¹OC(O)NR¹⁰-, and
 c) C₁₋₆ alkyl substituted by C₁₋₆ perfluoroalkyl, R¹⁰O-,
 R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

25 R¹⁰ is independently selected from hydrogen, C₁₋₆ alkyl, benzyl and
 aryl;

R¹¹ is independently selected from C₁₋₆ alkyl and aryl;

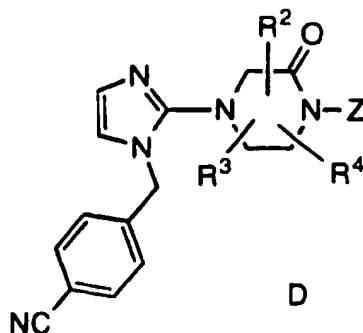
30 Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl,
 mono- or bicyclic arylmethyl, mono- or bicyclic
 heteroaryl, mono- or bicyclic arylsulfonyl,
 mono- or bicyclic heteroarylsulfonyl, unsubstituted or
 substituted with one or two of the following:

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- 1) C₁-4 alkyl, unsubstituted or substituted with:
- a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR⁶,
- 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 9) -S(O)_mR⁶,
- 10) -C(O)NR⁶R⁷, or
- 11) C₃-C₆ cycloalkyl;
- m is 0, 1 or 2; and

or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention,
the inhibitors of farnesyl-protein transferase are illustrated by the
formula D:



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wherein:

R², R³ and R⁴ are independently selected from: hydrogen or C₁-C₆ alkyl;

5

Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic heteroarylmethyl, mono- or bicyclic arylsulfonyl, mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:

10

1) C₁-4 alkyl, unsubstituted or substituted with:

a) C₁-4 alkoxy,

b) NR⁶R⁷,

c) C₃-6 cycloalkyl,

15

d) aryl or heterocycle,

e) HO,

f) -S(O)_mR⁶, or

g) -C(O)NR⁶R⁷,

2) aryl or heterocycle,

20

3) halogen,

4) OR⁶,

5) NR⁶R⁷,

6) CN,

7) NO₂,

25

8) CF₃;

9) -S(O)_mR⁶,

10) -C(O)NR⁶R⁷, or

11) C₃-C₆ cycloalkyl;

30

m is

0, 1 or 2; and

or the pharmaceutically acceptable salts thereof.

The preferred compounds of this invention are as follows:

35

- 25 -

4-[1-(4-methoxybenzyl)imidazol-2-yl]-1-(2-chlorophenyl)-piperazin-2-one and

4-[3-(4-methoxybenzyl)pyrid-4-yl]-1-(2-chlorophenyl)-piperazin-2-one

5

or the pharmaceutically acceptable salts or optical isomers thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R¹, R² etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring

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may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, 5 benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazoliny, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholiny, 10 naphthyridiny, oxadiazolyl, 2-oxoazepiny, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyraziny, pyrazolidiny, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydroquinoliny, 15 thiamorpholiny, thiamorpholiny sulfoxide, thiazolyl, thiazoliny, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four 20 carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, 25 dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indoliny, indolyl, isochromanyl, isoindoliny, isoquinoliny, isothiazolyl, naphthyridiny, oxadiazolyl, pyridyl, pyraziny, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, 30 tetrahydroisoquinoliny, tetrahydroquinoliny, thiazolyl, thienofuryl, thienothienyl, and thienyl.

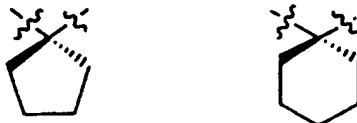
As used herein in the definition of R² and R³, the term "the substituted group" intended to mean a substituted C₁₋₈ alkyl, substituted

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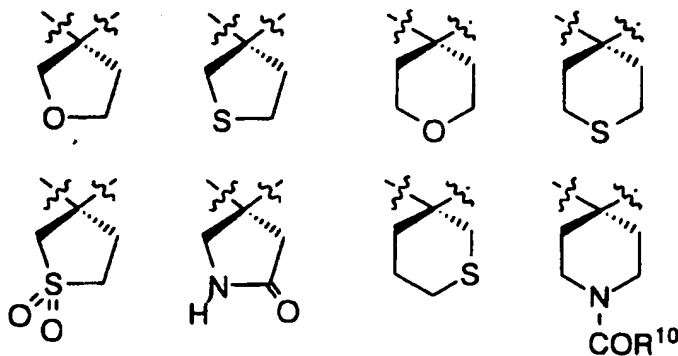
C₂-8 alkenyl, substituted C₂-8 alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R² and R³ are selected.

As used herein in the definition of R⁶, R^{6a}, R⁷ and R^{7a}, the substituted C₁-8 alkyl, substituted C₃-6 cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, such substituents are selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆ alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C₁-C₂₀ alkyl.

When R² and R³ are combined to form - (CH₂)_u -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:



In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

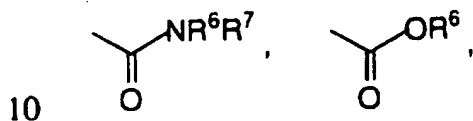


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Lines drawn into the ring systems from substituents (such as from R^2 , R^3 , R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

- Preferably, R^{1a} is selected from: hydrogen, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}$ - or unsubstituted or substituted C_1 - C_6 alkyl wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O$ - and $R^{10}C(O)NR^{10}$ -.

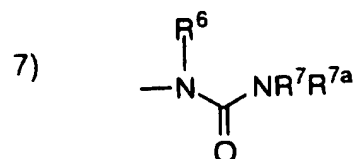
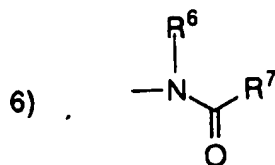
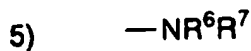
Preferably, R^2 is selected from: H,



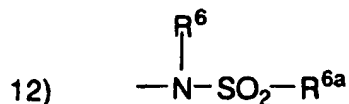
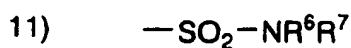
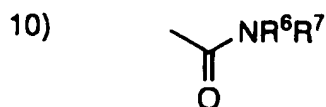
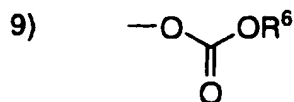
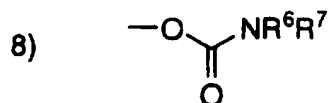
and an unsubstituted or substituted group, the group selected from C_1 -8 alkyl, C_2 -8 alkenyl and C_2 -8 alkynyl;

wherein the substituted group is substituted with one or more of:

- 15
- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C_1 -4 alkyl,
 - b) $(CH_2)_pOR^6$,
 - c) $(CH_2)_pNR^6R^7$,
 - d) halogen,
 - 20
 - 2) C_3 -6 cycloalkyl,
 - 3) OR^6 ,
 - 4) SR^{6a} , $S(O)R^{6a}$, SO_2R^{6a} ,



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5 Preferably, R^3 is selected from: hydrogen and $\text{C}_1\text{—C}_6$ alkyl.
 Preferably, R^4 is hydrogen.

Preferably, R^6 , R^7 and R^{7a} is selected from: hydrogen, unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

10 Preferably, R^{6a} is unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^9 is hydrogen or methyl. Most preferably, R^9 is hydrogen.

- 30 -

Preferably, R¹⁰ is selected from H, C₁-C₆ alkyl and benzyl.

Preferably, A¹ and A² are independently selected from: a bond, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-, -S(O)₂N(R¹⁰)- and-
 5 N(R¹⁰)S(O)₂-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, Y is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or
 10 substituted pyridyl, unsubstituted or substituted furanyl and unsubstituted or substituted thienyl. More preferably, Y is unsubstituted or substituted phenyl.

Preferably, Z is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or
 15 substituted pyridyl, unsubstituted or substituted furanyl and unsubstituted or substituted thienyl. More preferably, Z is unsubstituted or substituted phenyl.

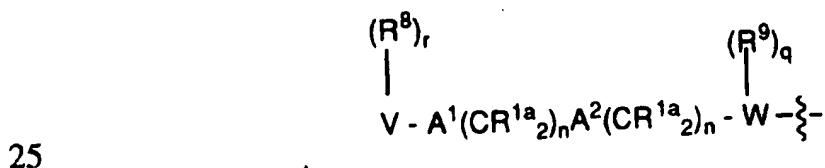
Preferably, W is selected from imidazolyl, imidazolyl, oxazolyl, pyrazolyl, pyrrolidinyl, thiazolyl and pyridyl. More
 20 preferably, W is selected from imidazolyl and pyridyl.

Preferably, n and r are independently 0, 1, or 2.

Preferably s is 0.

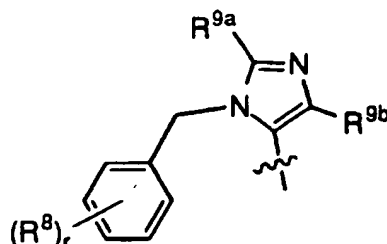
Preferably q is 1.

Preferably, the moiety



is selected from:

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It is intended that the definition of any substituent or variable (e.g., R^{1a} , R^9 , n , etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents $-NHH$, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

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Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-22, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R², R³, R⁴, and R⁵; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-16:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of suitably substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., 1990, 22, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-aryl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexylcarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV.

Scheme 2 illustrates the incorporation of a heterocyclic moiety on the remaining unsubstituted nitrogen of the piperazine. Thus, intermediate IV is treated with the isothiocyanate V, followed by methylation provides the thioimidate VI. Displacement of the methyl

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thiol moiety with an appropriately substituted amine followed by cyclization provides the N-imidazolyl piperazine VIII.

Scheme 2a illustrates incorporation of the preferred imidazolyl moiety on a nitrogen of a piperazinone. Thus, a suitably substituted aniline is N-alkylated sequentially with a protected acetaldehyde and a haloacetyl moiety. Reductive alkylation with an aminoimidazole, followed by base treatment provides the 1-phenyl-4-imidazolyl-piperazin-2-one. The imidazolyl can then be substituted with a suitably substituted benzyl moiety.

Preparation of the corresponding N-pyridyl piperazine XII is illustrated in Scheme 3. A suitably substituted benzaldehyde is coupled to 4-chloropyridine to provide the pyridylphenylmethanol IX. Removal of the hydroxyl moiety followed by oxidation of the pyridinyl nitrogen provide intermediate X. Intermediate X is then reacted with the piperazine IV to provide the instant compound XII.

Depending on the identity of the amino acid I, various side chains can be incorporated into the piperazine. For example when I is the Boc-protected β -benzyl ester of aspartic acid, the intermediate diketopiperazine XIII where $n=1$ and $R=\text{benzyl}$ is obtained, as shown in Scheme 4. Subsequent lithium aluminum hydride reduction reduces the ester to the alcohol XIV, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XV can then be carried on to final products as described in Schemes 2 and 3.

Reaction Scheme 5 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^2 and R^3 are combined to form $-(CH_2)_u-$. For example, 1-aminocyclohexane-1-carboxylic acid XVI can be converted to the spiropiperazine XVIII essentially according to the procedures outlined in Schemes 1. The piperazine intermediate XVIII can be carried on to final products as described in Schemes 2-3.

Scheme 6 illustrates the use of an optionally substituted homoserine lactone XXI to prepare a Boc-protected piperazinone

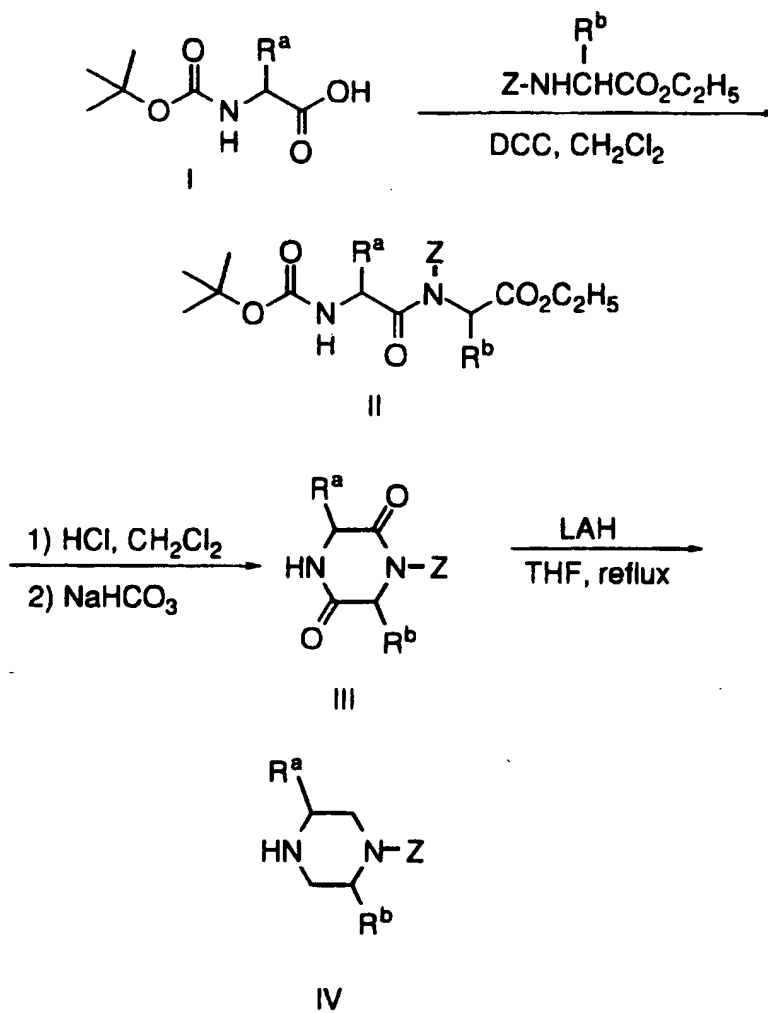
- 34 -

XXII. Intermediate XXII may be reduced, deprotected and reductively alkylated or acylated as illustrated in the previous Schemes.

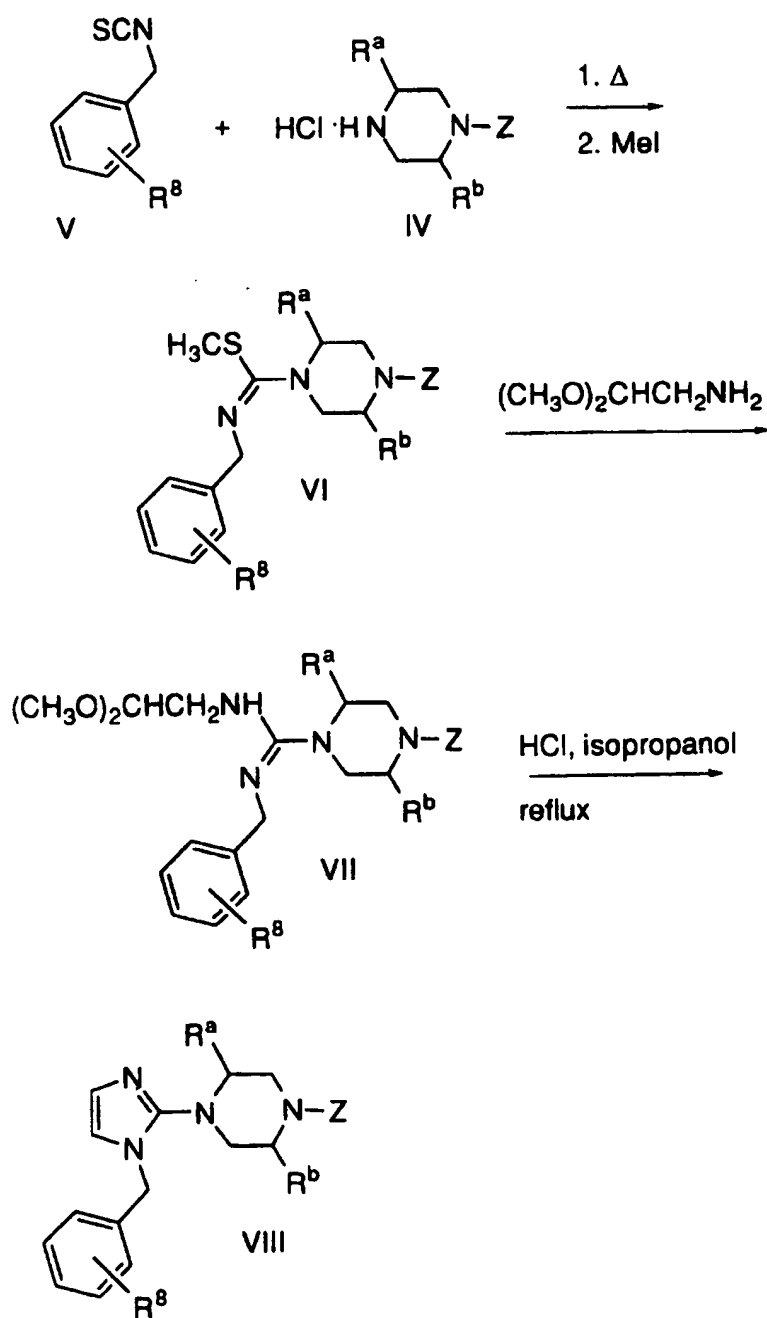
Alternatively, the hydroxyl moiety of intermediate XXIII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate XXIV. Intermediate XXIII may also be oxidized to provide the carboxylic acid on intermediate XXV, which can be utilized form an ester or amide moiety.

Amino acids of the general formula XXVI which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 18 starting with the readily prepared imine XXVII.

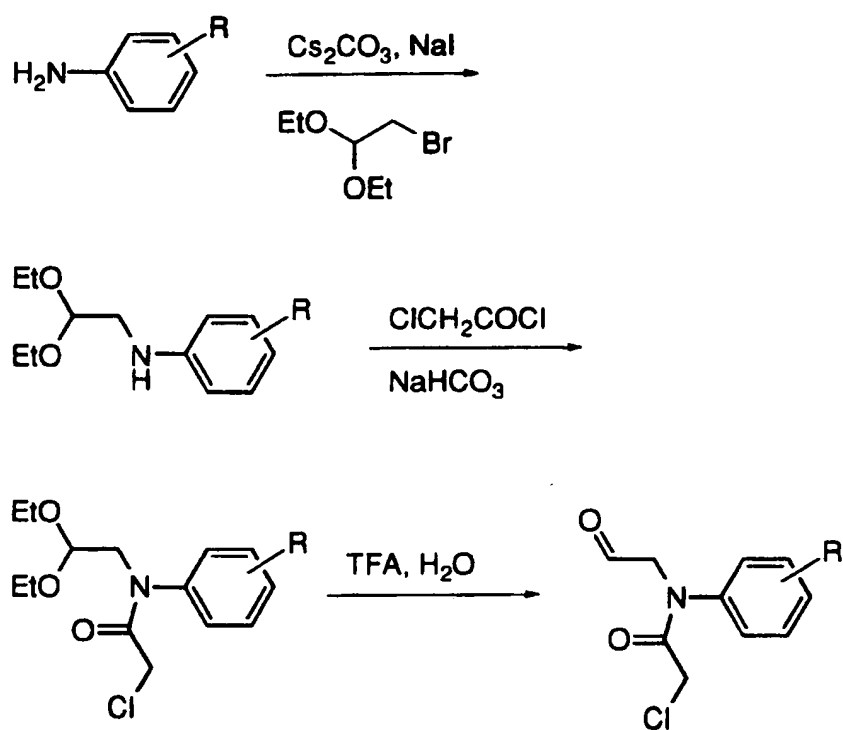
- 35 -

SCHEME 1

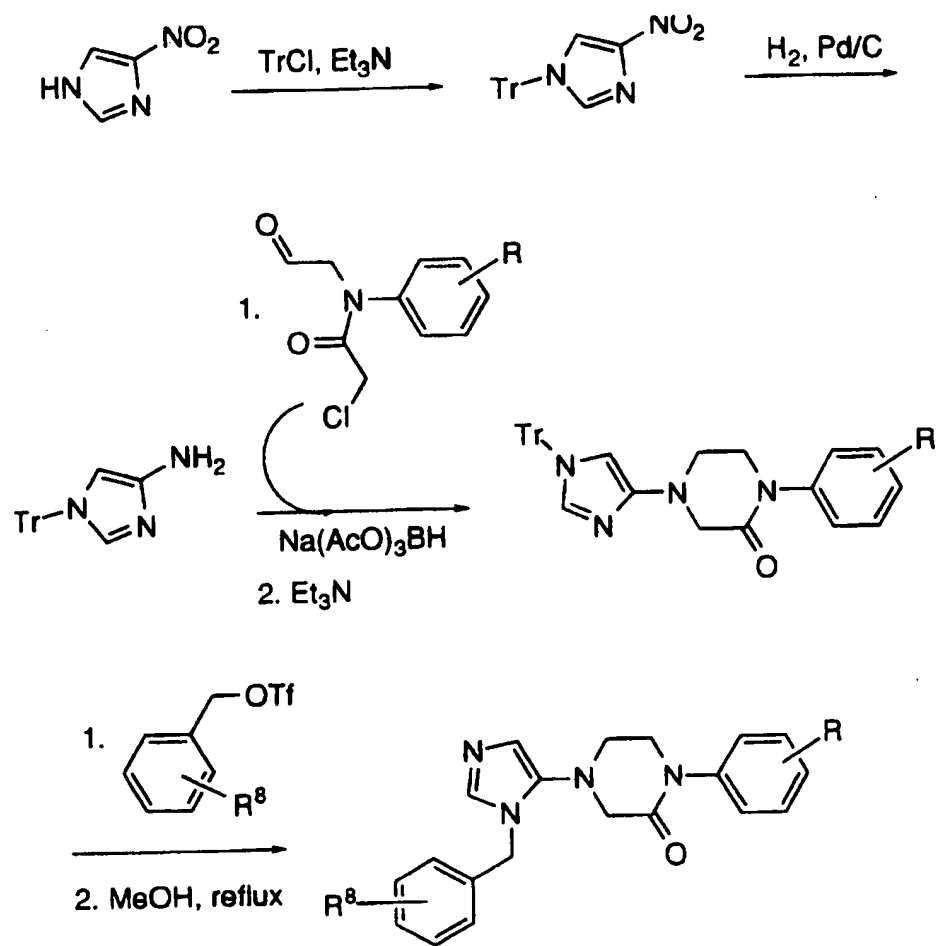
- 36 -

SCHEME 2

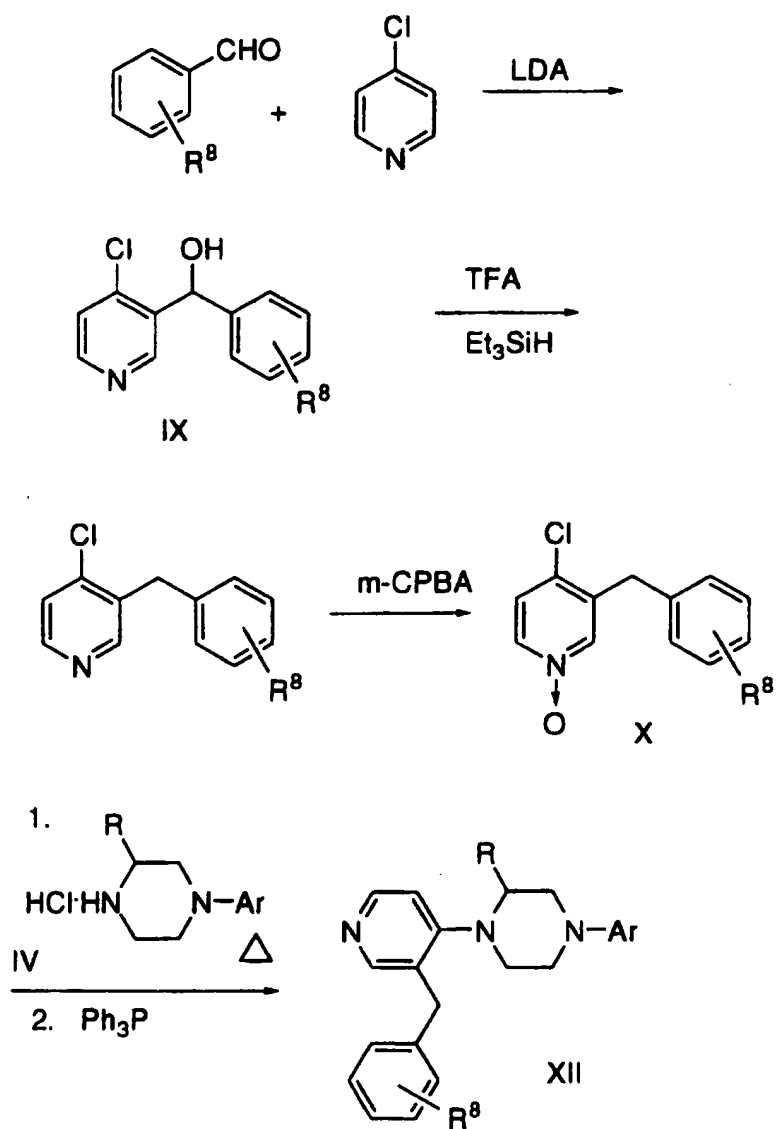
- 37 -

SCHEME 2a

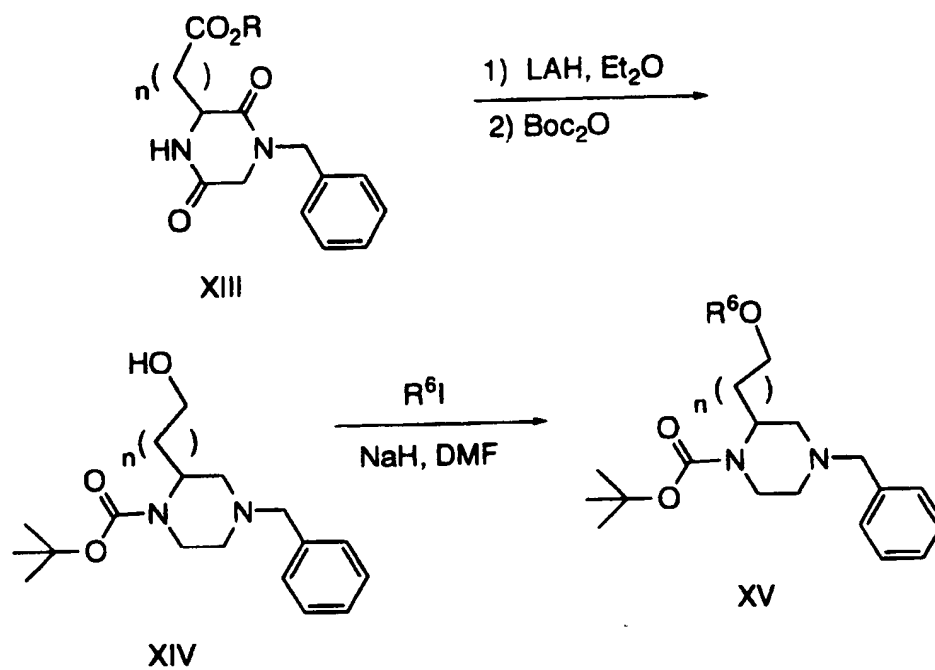
- 38 -

SCHEME 2a (continued)

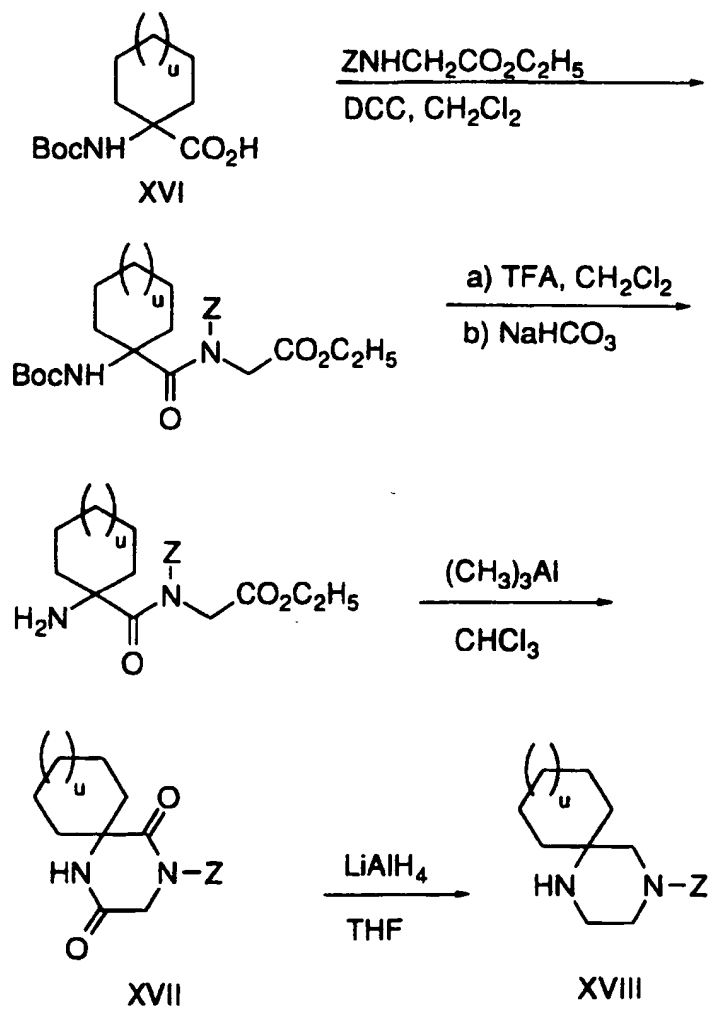
- 39 -

SCHEME 3

- 40 -

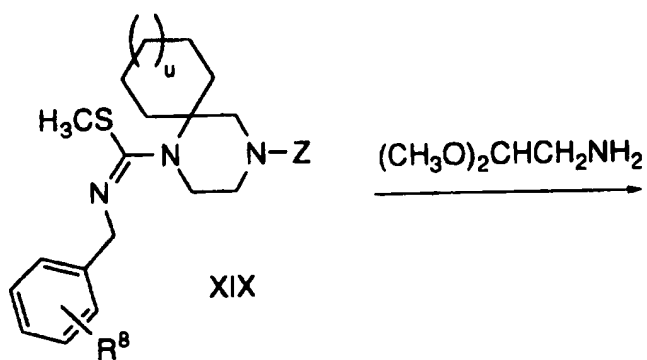
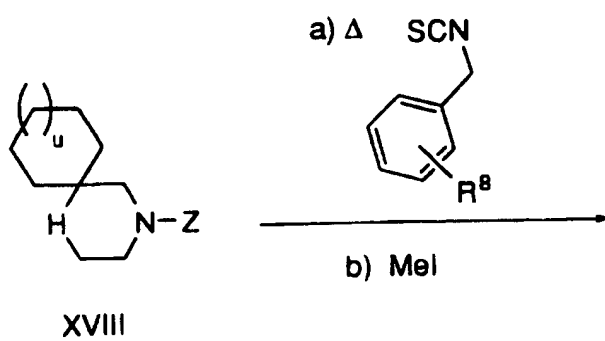
SCHEME 4

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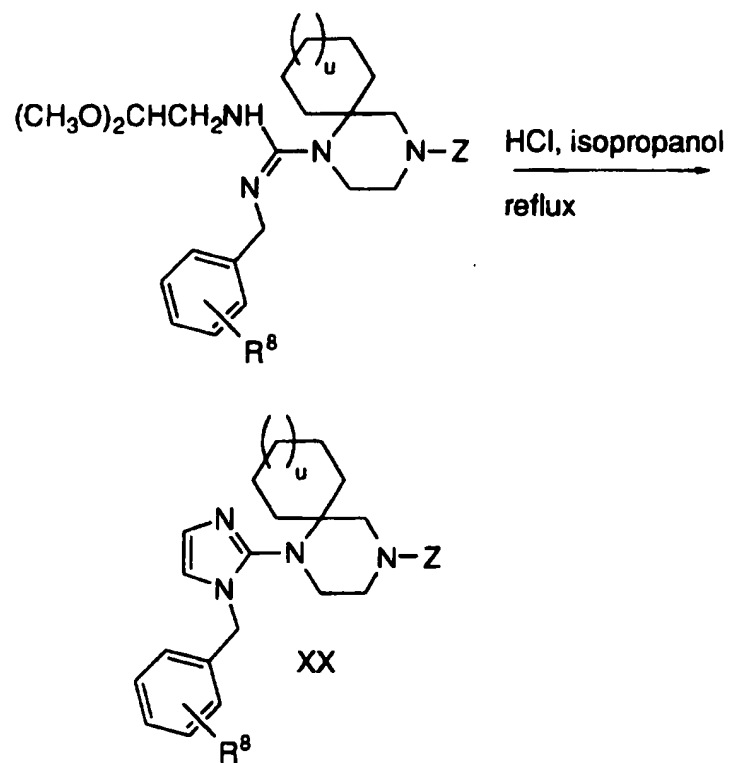
SCHEME 5

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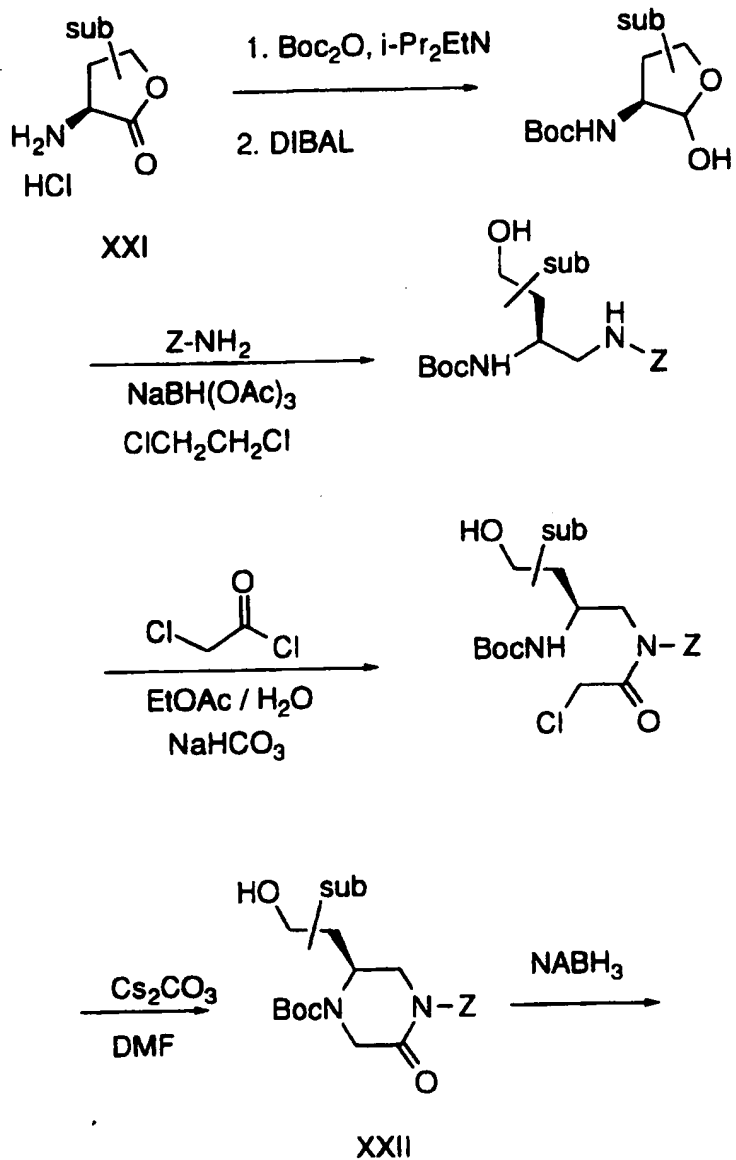
SCHEME 5 (continued)



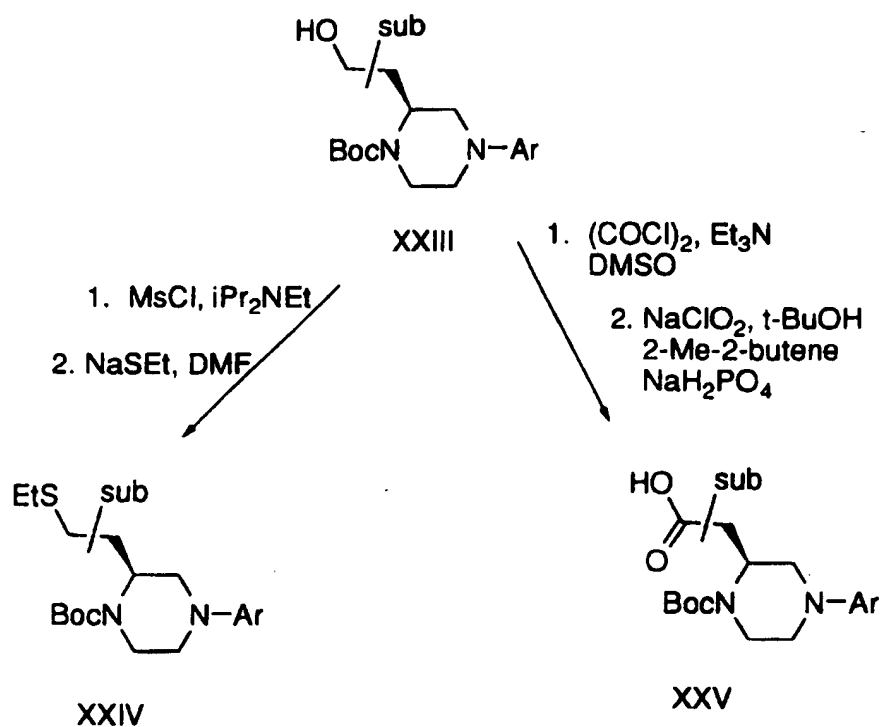
- 43 -

SCHEME 5 (continued)

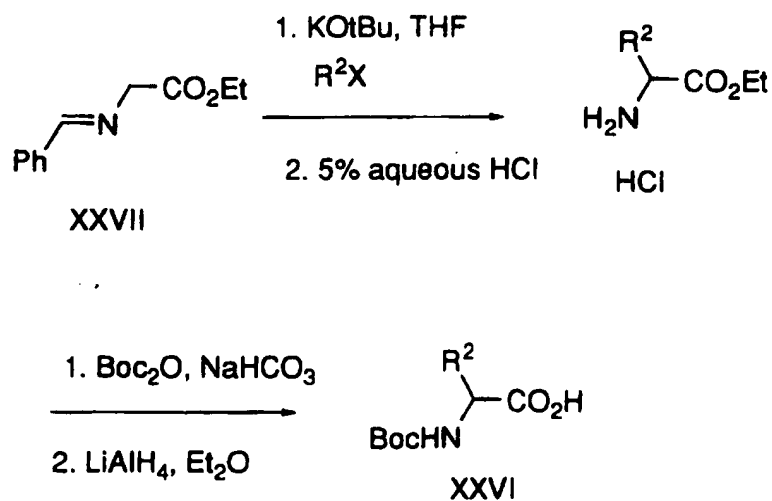
- 44 -

SCHEME 6

- 45 -

SCHEME 6 (continued)

5

SCHEME 7

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The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

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American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

5 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be
10 administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for
15 example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn
20 starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the
25 solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected
30 for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restenosis, polycystic kidney

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disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and

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quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a K_i substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

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EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species
5 and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

10 Preparation of 4-[1-(4-methoxybenzyl)imidazol-2-yl]-1-(2-chlorophenyl)-piperazin-2-one.

Step A: Synthesis of 4-[5-(4-methoxyphenyl)-2-thia-4-aza-pent-3-en-3-yl]-1-(2-chlorophenyl)-piperazin-2-one

15 Modifying the method of Poisson, et al., (Tetrahedron Letters 32, 5325 (1991)), p-methoxybenzyl isothiocyanate (1 molar equivalent) and 1-(2-chlorophenyl)-piperazine-2-one are heated in toluene at 50°C for 6 h. Without purification the product is S-methylated by treatment with methyl iodide (3 molar equivalents) to furnish
20 the title compound.

Step B: 4-[1-(4-methoxybenzyl)-imidazol-2-yl]-1-(2-chlorophenyl)-piperazin-2-one.

25 The product of step A is treated with aminoacetaldehyde dimethyl acetal (1.5 molar equivalents) in isopropanol. The intermediate guanidine is refluxed in isopropanol and hydrochloric acid to give the title compound.

EXAMPLE 2

30 Preparation of 4-[3-(4-methoxybenzyl)pyrid-4-yl]-1-(2-chlorophenyl)-piperazin-2-one.

Step A: 4-Chloro-3-(4-methoxybenzyl)pyridine.

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4-Chloropyridine is treated sequentially with LDA (1.1 molar equivalents) and 4-methoxybenzaldehyde (1 molar equivalent). The resulting carbinol is isolated and deoxygenated with triethylsilane (10 molar equivalents) and 50% trifluoroacetic acid in methylene chloride to provide the title compound.

Step B: 4-Chloro-3-(4-methoxybenzyl)pyridine-N-oxide

The product of step A is oxidized to the title compound with m-chloroperoxybenzoic acid (1.1 molar equivalents).

Step C: 4-[3-(4-methoxybenzyl)pyrid-4-yl]-1-(2-chlorophenyl)-piperazin-2-one.

The product of step B is heated with 1-(2-chlorophenyl)-piperazin-2-one (1 molar equivalent). The crude N-oxide of 4-[3-(4-methoxybenzyl)pyrid-4-yl]-1-(2-chlorophenyl)-piperazin-2-one is deoxygenated by treatment with triphenylphosphine (2 molar equivalents) to provide the title compound.

EXAMPLE 3

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber *et al.*, J. Biol. Chem. 265:14701-14704 (1990), Pompliano, *et al.*, Biochemistry 31:3800 (1992) and Gibbs *et al.*, PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μ l containing 100 mM N-(2-hydroxy ethyl) piperazine-N'-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl₂, 5 mM dithiothreitol (DTT), 100 mM [³H]-farnesyl diphosphate ([³H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μ g/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB β -

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plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^3H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM ZnCl_2 and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention are tested for inhibitory activity against human FPTase by the assay described above.

EXAMPLE 4

20

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi [^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl_2 /1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers

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of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a
5 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front
10 reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

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EXAMPLE 5

In vivo growth inhibition assay

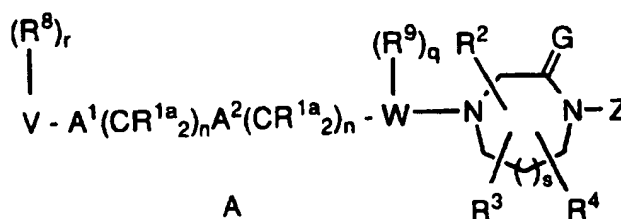
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a
20 *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by *v-Raf* and *v-Mos* maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos*
25 are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in
30 methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:

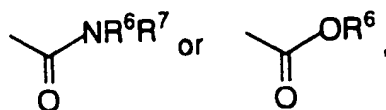


wherein:

R^{1a} is selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)NR¹⁰-;

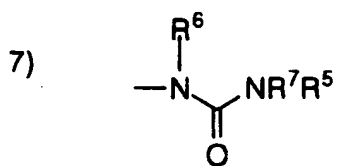
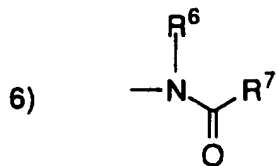
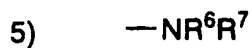
R² and R³ are independently selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



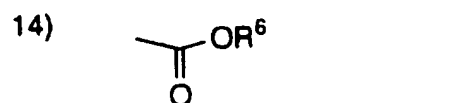
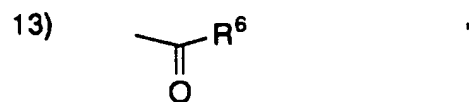
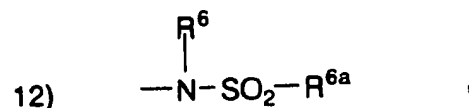
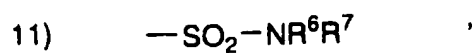
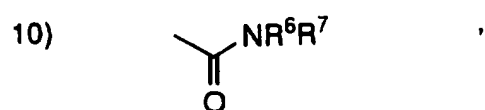
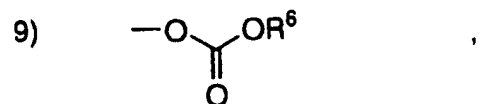
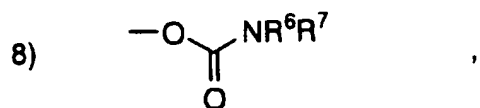
- 55 -

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁₋₄ alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁₋₄ alkyl, or
 - h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃₋₆ cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



- 56 -



- 5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

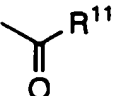
R^4 is selected from H and CH_3 ;

10

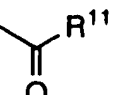
and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

- 57 -

R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 5 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 10 g) N(R¹⁰)₂; or

R⁶ and R⁷ may be joined in a ring;
 R⁷ and R^{7a} may be joined in a ring;

- 15 R^{6a} is selected from: C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl,
 unsubstituted or substituted with:
- a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 20 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 g) N(R¹⁰)₂;

- 25 R⁸ is independently selected from:
- a) hydrogen,
 b) aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl,

- 58 -

- C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 5 c) C1-C6 alkyl unsubstituted or substituted by aryl,
 cyanophenyl, heterocycle, C3-C10 cycloalkyl, C2-C6
 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 10 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- 15 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 20 c) C1-C6 alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C1-C6 alkyl, benzyl and
 aryl;

25

R¹¹ is independently selected from C1-C6 alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
 30 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

G is selected from H₂ and O;

V is selected from:

- 59 -

- 5
- a) hydrogen,
 - b) heterocycle,
 - c) aryl,
 - d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 - e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

10

W is a heterocycle;

15 Z is selected from: a unsubstituted or substituted group selected from aryl or heteroaryl, wherein the substituted group is substituted with one or more of the following:

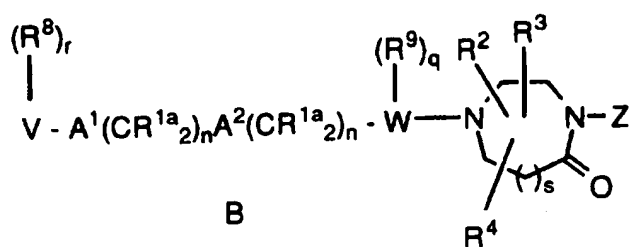
- a) C₁-4 alkyl, unsubstituted or substituted with: C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
- b) aryl or heterocycle,
- 20 c) halogen,
- d) OR⁶,
- e) NR⁶R⁷,
- f) CN,
- 25 g) NO₂,
- h) CF₃;
- i) -S(O)_mR^{6a},
- j) -C(O)NR⁶R⁷, or
- k) C₃-C₆ cycloalkyl; ;

30 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 q is 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen; and
 s is 0 or 1;

- 60 -

or a pharmaceutically acceptable salt thereof.

2. A compound which inhibits farnesyl-protein
5 transferase of the formula B:

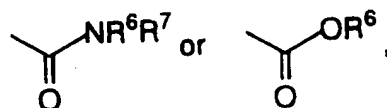


wherein:

R^{1a} is selected from:

- 10 a) hydrogen,
b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,
C₂-C₆ alkynyl, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
(R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-,
N₃, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-,
15 c) unsubstituted or substituted C₁-C₆ alkyl wherein the
substituent on the substituted C₁-C₆ alkyl is selected from
unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀
cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R¹⁰O-,
R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, and R¹¹OC(O)-
20 NR¹⁰-.;

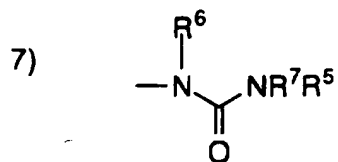
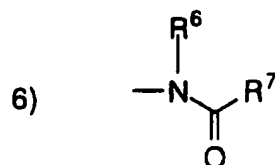
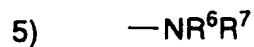
- R² and R³ are independently selected from: H; unsubstituted or
substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl,
unsubstituted or substituted C₂-8 alkynyl, unsubstituted or substituted aryl,
25 unsubstituted or substituted heterocycle,



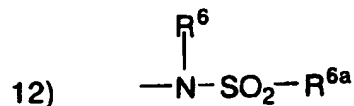
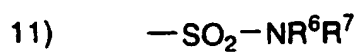
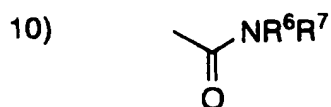
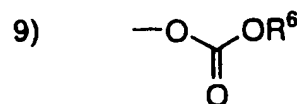
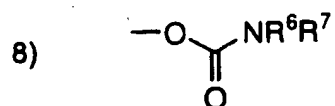
- 61 -

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) C₁₋₄ alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - g) perfluoro-C₁₋₄ alkyl, or
 - h) SR^{6a}, S(O)R^{6a}, SO₂R^{6a},
- 2) C₃₋₆ cycloalkyl,
- 3) OR⁶,
- 4) SR^{6a}, S(O)R^{6a}, or SO₂R^{6a},



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- 5 R^2 and R^3 are attached to the same C atom and are combined to form $(\text{CH}_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , —NC(O)— , and $\text{—N(COR}^{10})\text{—}$;

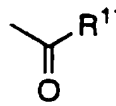
R^4 is selected from H and CH_3 ;

10

and any two of R^2 , R^3 and R^4 are optionally attached to the same carbon atom;

- 63 -

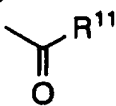
R⁶, R⁷ and R^{7a} are independently selected from: H; C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 5 a) C₁-4 alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 g) N(R¹⁰)₂; or

10

R⁶ and R⁷ may be joined in a ring;
 R⁷ and R^{7a} may be joined in a ring;

15 R^{6a} is selected from: C₁-4 alkyl, C₃-6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,
 e) 
 f) —SO₂R¹¹ , or
 g) N(R¹⁰)₂;

20

R⁸ is independently selected from:

- 25 a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl,

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- C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 5 c) C1-C6 alkyl unsubstituted or substituted by aryl,
 cyanophenyl, heterocycle, C3-C10 cycloalkyl, C2-C6
 alkenyl, C2-C6 alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NH-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 10 R¹⁰OC(O)NH-;

R⁹ is selected from:

- a) hydrogen,
- 15 b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, R¹⁰O-,
 R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)-, R¹⁰₂N-
 C(NR¹⁰)-, CN, NO₂, R¹⁰C(O)-, N₃, -N(R¹⁰)₂, or
 R¹¹OC(O)NR¹⁰-, and
- 20 c) C1-C6 alkyl unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R¹⁰O-, R¹¹S(O)_m-, R¹⁰C(O)NR¹⁰-,
 (R¹⁰)₂NC(O)-, R¹⁰₂N-C(NR¹⁰)-, CN, R¹⁰C(O)-, N₃,
 -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R¹⁰ is independently selected from hydrogen, C1-C6 alkyl, benzyl and
 aryl;

25

R¹¹ is independently selected from C1-C6 alkyl and aryl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR¹⁰-, -NR¹⁰C(O)-, O, -N(R¹⁰)-,
 30 -S(O)₂N(R¹⁰)-, -N(R¹⁰)S(O)₂-, or S(O)_m;

V is selected from:

- a) hydrogen,
 b) heterocycle,

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- c) aryl,
 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
 5 e) C₂-C₂₀ alkenyl,
 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

W is a heterocycle;

10

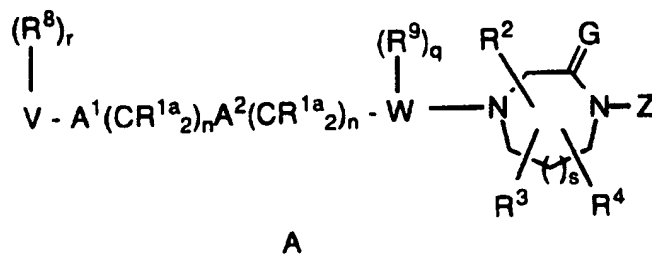
Z is selected from: a unsubstituted or substituted group selected from aryl or heteroaryl, wherein the substituted group is substituted with one or more of the following:

- 15 a) C₁-4 alkyl, unsubstituted or substituted with:
 C₁-4 alkoxy, NR⁶R⁷, C₃-6 cycloalkyl, aryl, heterocycle, HO, -S(O)_mR^{6a}, or -C(O)NR⁶R⁷,
 b) aryl or heterocycle,
 c) halogen,
 d) OR⁶,
 20 e) NR⁶R⁷,
 f) CN,
 g) NO₂,
 h) CF₃;
 i) -S(O)_mR^{6a},
 25 j) -C(O)NR⁶R⁷, or
 k) C₃-C₆ cycloalkyl; ;

- m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
 30 q is 1 or 2;
 r is 0 to 5, provided that r is 0 when V is hydrogen; and
 s is 1;

or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula A:



wherein:

5

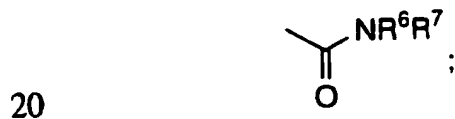
R1a is independently selected from: hydrogen or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 10 a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl,
15 alkenyl, $R^{10}O-$ and $-N(R^{10})_2$;

R³ and R⁴ are independently selected from H and CH₃;

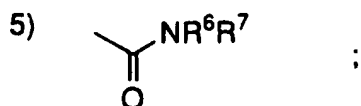
R^2 is H ;



or C1-5 alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

- 25 1) aryl,
 2) heterocycle,
 3) OR⁶,
 4) SR^{6a}, SO₂R^{6a}, or

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and any two of R², R³, R⁴, and R⁵ are optionally attached to the same carbon atom;

5 R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

- 10 a) C₁₋₄ alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:

C₁₋₄ alkyl or C₃₋₆ cycloalkyl,
unsubstituted or substituted with:

- 15 a) C₁₋₄ alkoxy,
b) halogen, or
c) aryl or heterocycle;

R⁸ is independently selected from:

- 20 a) hydrogen,
b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂,
(R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
R¹¹OC(O)NR¹⁰-, and
25 c) C₁₋₆ alkyl substituted by C₁₋₆ perfluoroalkyl, R¹⁰O-,
R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-,
-N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

R⁹ is selected from:

- 30 a) hydrogen,
b) C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ perfluoroalkyl,

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F, Cl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, CN, NO_2 ,
 $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$, and

- 5 c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6
 perfluoroalkyl, F, Cl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$,
 CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $-N(R^{10})_2$, or
 $R^{11}OC(O)NR^{10}-$;

10 R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and
 aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

15 A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$,
 $-C(O)-$, $-C(O)NR^{10}-$, O, $-N(R^{10})-$, or $S(O)_m$;

G is selected from H_2 and O;

V is selected from:

- 20 a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl,
 pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl,
 quinolinyl, isoquinolinyl, and thienyl,
 c) aryl,
 25 d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are
 replaced with a heteroatom selected from O, S, and N,
 and
 e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen
 30 if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl,
 thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or
 isoquinolinyl;

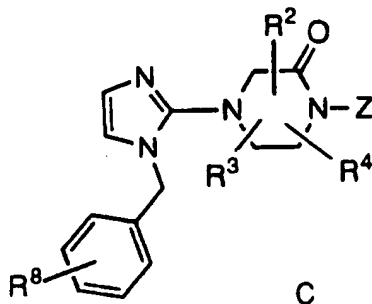
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- Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl,
mono- or bicyclic arylmethyl, mono- or bicyclic
heteroarylmethyl, mono- or bicyclic arylsulfonyl,
5 mono- or bicyclic heteroarylsulfonyl, unsubstituted or
substituted with one or two of the following:
- 1) C₁₋₄ alkyl, unsubstituted or substituted with:
 - a) C₁₋₄ alkoxy,
 - b) NR⁶R⁷,
 - 10 c) C₃₋₆ cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
 - 15 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR⁶,
 - 5) NR⁶R⁷,
 - 6) CN,
 - 20 7) NO₂,
 - 8) CF₃;
 - 9) -S(O)_mR⁶,
 - 10) -C(O)NR⁶R⁷, or
 - 11) C₃₋₆ cycloalkyl;
- 25 m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
30 s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

or a pharmaceutically acceptable salt thereof.

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4. The compound according to Claim 1 of the formula C:

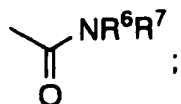


wherein:

5

R^3 and R^4 are independently selected from H and CH_3 ;

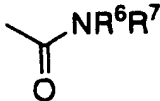
R^2 is H;



10

or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

15

- 1) aryl,
- 2) heterocycle,
- 3) OR^6 ,
- 4) SR^{6a} , SO_2R^{6a} , or
- 5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

20 R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C_{1-4} alkoxy,
- b) halogen, or

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c) aryl or heterocycle;

R^{6a} is selected from:

- 5 C₁-4 alkyl or C₃-6 cycloalkyl,
 unsubstituted or substituted with:
- a) C₁-4 alkoxy,
 - b) halogen, or
 - c) aryl or heterocycle;

10 **R⁸** is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, CN, NO₂, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or
- 15 R¹¹OC(O)NR¹⁰-, and
- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R¹⁰O-, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂N-C(NR¹⁰)-, R¹⁰C(O)-, -N(R¹⁰)₂, or R¹¹OC(O)NR¹⁰-;

20 **R¹⁰** is independently selected from hydrogen, C₁-C₆ alkyl, benzyl and aryl;**R¹¹** is independently selected from C₁-C₆ alkyl and aryl;25 **Z** is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic heteroarylmethyl, mono- or bicyclic arylsulfonyl, mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:

- 30 1) C₁-4 alkyl, unsubstituted or substituted with:
- a) C₁-4 alkoxy,
 - b) NR⁶R⁷,
 - c) C₃-6 cycloalkyl,
 - d) aryl or heterocycle,

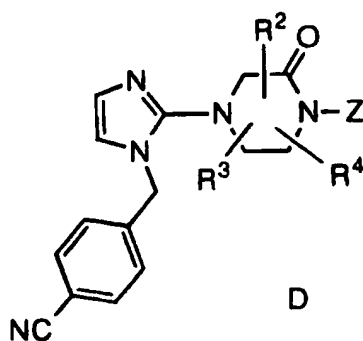
- 72 -

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 10
 15
- e) HO,
 - f) $-S(O)_mR^6$, or
 - g) $-C(O)NR^6R^7$,
 - 2) aryl or heterocycle,
 - 3) halogen,
 - 4) OR^6 ,
 - 5) NR^6R^7 ,
 - 6) CN,
 - 7) NO_2 ,
 - 8) CF_3 ;
 - 9) $-S(O)_mR^6$,
 - 10) $-C(O)NR^6R^7$, or
 - 11) C_3-C_6 cycloalkyl;

15 m is 0, 1 or 2; and

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 of the formula D:



20

wherein:

R^2 , R^3 and R^4 are independently selected from: hydrogen or C_1-C_6 alkyl;

25

Z is mono- or bicyclic aryl, mono- or bicyclic heteroaryl, mono- or bicyclic arylmethyl, mono- or bicyclic

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heteroarylmethyl, mono- or bicyclic arylsulfonyl, mono- or bicyclic heteroarylsulfonyl, unsubstituted or substituted with one or two of the following:

- 1) C₁₋₄ alkyl, unsubstituted or substituted with:
 - a) C₁₋₄ alkoxy,
 - b) NR⁶R⁷,
 - c) C₃₋₆ cycloalkyl,
 - d) aryl or heterocycle,
 - e) HO,
 - f) -S(O)_mR⁶, or
 - g) -C(O)NR⁶R⁷,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) OR⁶,
- 5) NR⁶R⁷,
- 6) CN,
- 7) NO₂,
- 8) CF₃;
- 9) -S(O)_mR⁶,
- 10) -C(O)NR⁶R⁷, or
- 11) C₃₋₆ cycloalkyl;

m is 0, 1 or 2; and

or a pharmaceutically acceptable salt thereof.

6. A compound which inhibits farnesyl-protein transferase which is:

4-[1-(4-methoxybenzyl)imidazol-2-yl]-1-(2-chlorophenyl)-piperazin-2-one or

4-[3-(4-methoxybenzyl)pyrid-4-yl]-1-(2-chlorophenyl)-piperazin-2-one

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or a pharmaceutically acceptable salt or optical isomer thereof.

7. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
5 amount of a compound of Claim 1.

8. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 2.

10 9. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 4.

15 10. A pharmaceutical composition comprising a
pharmaceutical carrier, and dispersed therein, a therapeutically effective
amount of a compound of Claim 6.

20 11. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 7.

25 12. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 8.

30 13. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 9.

14. A method for inhibiting farnesyl-protein transferase
which comprises administering to a mammal in need thereof a
therapeutically effective amount of a composition of Claim 10.

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15. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

5 16. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

10 17. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

15 18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

20 19. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

25 20. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

21. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

30 22. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

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23. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

5 24. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

10 25. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05049

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/495; C07D 403/04

US CL : 514/255; 544/370

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/255; 544/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Structure Search - files Registry and CAPIus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,461,059 A (BONNET et al.) 24 October 1995.	1-25
A	US 5,256,665 A (ORJALES-VENERO et al.) 26 October 1993.	1-25
A	ORJALES et al. Synthesis and structure-activity relationship of new piperidinyl and piperazinyl derivatives as antiallergics. Journal of Heterocyclic Chemistry. May-June 1995, Vol. 32, pages 707-718.	1-25
A	EP 0 628 549 A1 (FABRICA ESPANOLA DE PRODUCTOS QUIMICOS Y FARMACEUTICOS, S.A. (FAES)). 14 December 1994.	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 22 MAY 1997	Date of mailing of the international search report 24 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD S. MYERS, JR. <i>for</i> Telephone No. (703) 305-1235